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1041-91 Oxygen Free Radical Scavengers Prevent Damage to Proteins of the Sarcomere Initiated by Reversible Ischemia/Reperfusion Injury

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Background: Prolonged contractile dysfunction is a characteristic feature of brief periods of ischemia with subsequent reperfusion, or myocardial stunning. It has been shown that a loss of calcium response of the myofilament may influence this loss of contractile function. In the past, myocardial stunning has also been attributed to the proteolysis of sarcomeric proteins. Such changes in contractile response have been reversed by the addition of oxygen free radical (OFR) scavengers.
Methods: Left ventricular (LV) samples were taken from rabbit hearts after either 75 min normal perfusion (control) or 15 min low flow (1 ml/min) ischemia followed by 60 min reperfusion (15I/60R) (n=6/group). A further group (n=6) underwent the 15I/60R protocol, but with the hydroxyl radical scavenger, N-(2-mercaptopropionyl) glycine (MPG, 3 mM) added to the perfusate (15I/60R+MPG). Isovolumetric LV pressure was measured throughout. Whole cell and myofilament-associated protein profiles were generated by two-dimensional gel electrophoresis and mass spectrometry was utilized to identify differentially abundant sarcomeric proteins as determined by image analysis.
Results: Rate pressure product at the end of the protocol was impaired in 15I/60R (61+6% baseline) in comparison to control (90±6%, mean ± SEM; p <0.01) but was preserved (106±9% baseline) in MPG treated hearts. Comparative analysis of control and stunned myocardium revealed modifications to multiple proteins of the sarcomere (>1.5-fold difference in visible abundance). Cleavage of MLC-2, α-actin 2, and a skeletal LIM domain protein as a consequence of 15I/60R was prevented by addition of MPG. The addition of MPG also abolished the removal of TnC from the myofilament-associated fraction following 15I/60R.
Discussion: The cleavage of essential protein constituents may contribute to impaired contractile function, which is characteristic of stunning. The removal of TnC from the myofilament may in part explain the reduced calcium response. With the addition of the OFR scavenger MPG we observed the prevention of these modifications, indicating that damage to sarcomeric proteins may be related to the presence of OH radicals during reperfusion.

1041-92 Calmodulin Kinase Inhibition Improves Cardiac Function After Myocardial Infarction

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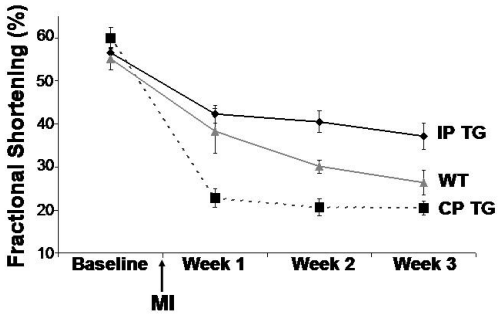
Background: Calmodulin kinase (CaMK) signaling is linked to cardiomyopathy and CaMK activity is increased in patients and animal models with cardiomyopathy from myocardial infarction (MI).
Methods: We created surgical MI by ligation of the left coronary artery in transgenic (TG) mice with genetic CaMK inhibition by cardiac expression of a specific CaMK inhibitory peptide, IP. TG mice expressing an inactive scrambled peptide, CP, and wild type (WT) littermates were used as controls. There was no difference in baseline heart weight/body weight ratios or left ventricular (LV) fractional shortening (FS) in age- and gender-matched mice.
Results: 3 weeks after MI, IP TG mice had relatively preserved LV function (FS = 37.2 ± 3.1%, n = 12) compared to CP TG mice (FS = 20.6 ± 1.6%, n = 10) and WT mice (FS = 26.4 ± 2.9%, n = 11, P < 0.001) (Figure). We measured ANP expression, a marker for cardiomyopathy, from whole hearts 3 weeks post-MI using real time PCR normalized to 18S and reported as relative increases in induction over non-infarcted WT hearts. ANP induction after MI was significantly reduced in IP TG mice (11 ± 2 fold, n = 4) compared to CP TG mice (23 ± 6 fold, n = 5) and WT mice (57 ± 16 fold, n = 4; P < 0.001). This rescue of LV function and heart failure was recapitulated in a dose-dependent manner with pharmacologic CaMK inhibition with KN-93 on WT mice.
Conclusion: Our results show that increased CaMK activity following MI is mechanistically linked to worsening cardiac function and that CaMK inhibition can preserve LV function after MI.



1041-93 Caspase Inhibition Reduces Calpain Activation and Calpain Induced Troponin-I Cleavage, Calpain Induced Cytochrome C Release and Apoptosis in the Postmyocardial Infarction Remodeling Myocardium

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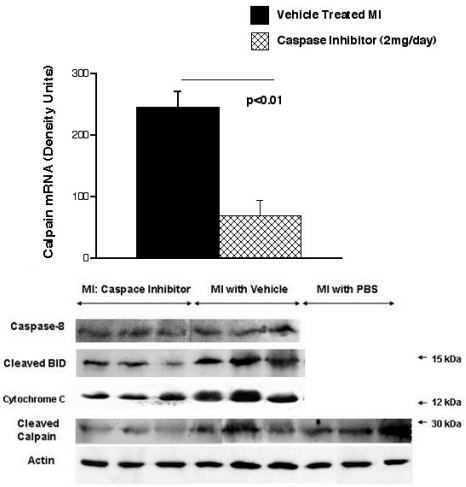
Background: Calpain mediates contractile failure via troponin-I cleavage but its role in heart failure is unclear.
Hypothesis: Caspases can cleave & activate Calpain. Calpain can then cleave Troponin-I to cause contractile failure & cleave BID to release Cytochrome C with subsequent apoptosis. Caspase inhibition [CI] should attenuate these changes.
Methods: MI rats were given a caspase inhibitor (zAsp-CH2-DCB, 2 mg/day IP x 30 days, started at surgery, n=12) or vehicle ([V], n=9). Calpain & Caspase activation, BID & troponin-I cleavage, & cytochrome C release were measured (westerns, n=6 each group) in peri MI region & correlated with apoptosis (Apologix Stain) & LV remodeling (Echo).
Results: Infarcts were 35±6% & similar in both groups. [V] showed Calpain activation & troponin-I cleavage accompanied by BID cleavage, cytochrome C release & apoptosis. CI reduced Calpain mRNA & protein. This was accompanied by less troponin-I cleavage & better systolic function [Fractional Shortening: 29±3% vs 19±2%, p<0.05]. CI also reduced BID cleavage resulting in less cytochrome C release without affecting Caspase 8. Apoptosis & ventricular remodeling [heart/body wt: 3.56±0.1 vs. 5.1±0.3, p<0.05] were less with CI.
Conclusions: Caspase inhibition reduces calpain activation resulting in less troponin-I cleavage & better function. CI also attenuates BID cleavage & cytochrome C mediated apoptosis via a Calpain dependent but Caspase 8 independent pathway. Calpain inhibition may have a role in benefits seen after CI.



1041-94 Noninvasive Evaluation of Coronary Artery Flow Using Transthoracic Color Doppler Echocardiograpy in Patients With Acute Myocardial Infarction in the Emergency Room

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Background: In the emergency room (ER), transthoracic color Doppler echocardiography (TCDE) and conventional echocardiography, assessing coronary artery blood flow (CBF) and detecting wall motion abnormality in patients (pts) with suspected acute myocardial infarction (AMI), is a noninvasive method for evaluating the coronary flow and cardiac anatomy of the left anterior descending coronary artery (LAD) territory, simultaneously.
We have reported that TCDE was useful for assessing CBF in the LAD. Spontaneous reperfusion before percutaneous coronary intervention (PCI) has reported to be an independent determinant of prognosis in pts with AMI. No and slow reflow of the LAD in AMI after PCI was considered adversely affecting the clinical outcomes. Aim of this study was to test the hypothesis that TCDE in the ER is feasible for estimating coronary occlusion or spontaneous reperfusion of the LAD and assessing the coronary flow velocity pattern such as no reflow pattern, which reported to be an important prognostic information in pts with AMI.
Method: Consecutive 90 pts with chest pain and wall motion abnormality in the LAD territory were enrolled in this study. Before coronary angiography, 34 out of 90 pts (38%, AMI 29, normal coronary 5) attempting TCDE to detect CBF, were divided into two groups, group A; diastolic CBF was detected in the culprit lesion (n=14), group B; diastolic CBF not detected (n=20). The in-hospital complications, max CPK, TIMI grade, ejection fraction and wall motion score index of the LV were compared between two groups.
Result: The sensitivity of detecting LAD flow was 13/14 (93%) in group A and LAD occlusion (undetected LAD flow corresponding TIMI grade 0 or 1) was 18/20 (94%) in group B. In group B, max CPK was significantly higher than in group A (4338±3239 vs. 845±690,